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L2 0 WO01091798/PN  
(WO1091798/PN)

=> s wo2001091798/pn  
L3 1 WO2001091798/PN  
(WO2001091798/PN)

=> s l3 and target?  
186329 TARGET?  
L4 1 L3 AND TARGET?

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25735 PROSTATE  
437 PROSTATES  
25750 PROSTATE  
(PROSTATE OR PROSTATES)  
34105 OVAR?  
34026 BREAST  
1455 BREASTS  
34301 BREAST  
(BREAST OR BREASTS)  
L5 1 L4 AND (PROSTATE OR OVAR? OR BREAST)

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L5 ANSWER 1 OF 1 PCTFULL COPYRIGHT 2006 Univentio on STN  
PI WO 2001091798 A2 20011206

ABEN . . . biologically active entity linked to a masking moiety <i>via</i>  
a linking moiety. The prodrug compounds are selectively activated at or  
near target cells and display lower toxicity and possibly a  
longer <i>in vivo</i> or serum half-life than the corresponding naked  
biologically active. . .

DETD . . . cleaved by proteases and/or peptidases in the  
extracellular medium at or near tumor cells and certain endothelial  
cells involved in  
20' neoangiogenesis ('target cells). Particularly, peptides  
that may be specifically cleaved in  
the target extracellular milieu include those having the amino  
acid sequence (Leu)<sup>y</sup>(Ala-  
Leu)<sub>x</sub>Ala-Leu and (Leu)<sup>y</sup>(Ala-Leu)<sub>x</sub>Ala-Phe, where y is 0 or 1 and x. . .  
invention together permits the biologically active  
entity to be selectively released or liberated in vivo at or near a  
tumor or target cell.

. . .  
by virtue  
of the linking moiety and the observed differences in the amount of  
specifically cleaving

peptidases produced and/or secreted by the target and healthy cells, the prodrugs of the invention permit compounds that are cytotoxic or cytostatic to be selectively delivered to the target celis, thereby providing a selective and safe means of delivering the cytotoxic and/or cytostatic agents to patients to treat turnorigenic conditions, . . .

facilitates transport into the cell or cell nucleus. Selective delivery of a biologically active entity directly into the nucleus of a target Gel&iecl; may improve the selectivity of the biologically active entity and may overcome drug resistance to the biologically active entity. Intracellularly active. . . the invention in which the biologically active entity includes a transport peptide permit selective delivery of biologically active entities to tumors and/or target celis that otherwise SUBSTITUTE SHEET (RULE 26) compositions of the invention in association with a transport peptide that acts to enhance its membrane. . .

tumor or a tumor cell or an endothelial cell involved in tumor neoangiogenesis. The method comprises contacting a tumor or a target cell with an amount of a prodrug or pharmaceutical composition of the invention effective to inhibit the growth or proliferation of the tumor cell or target cell. The method can be practiced to inhibit the growth or proliferation of tumors and/or target celis in vivo, in vitro or ex vivo.

313 illustrates the specific cleavage of a prodrug of one polarity in the extracellular milieu at or near a tumor or target cell; FIG. 3C illustrates the specific cleavage of a prodrug of a second polarity in the extracellular milieu at or near a tumor or target cell SUBSTITUTE SHEET (RULE 26) FIG. 3D illustrates the specific cleavage of a prodrug comprising a spacing moiety; FIG. 3E illustrates the specific. . .

'Biologically active entity' refers to a molecule or construct that exerts a biological effect on a target cell, as defined herein. Typically, the entity is cytotoxic and/or cytostatic toward target celis or sensitizes target celis to the action of another cytotoxic or cytostatic entity.

active entity to a masking moiety and that is susceptible to specific, selective cleavage at or near a tumor or a target cell, as defined herein.

11 Selective cleavage` refers to the enhanced or preferential specific cleavage achieved at or near a target cell. Thus, while the specific cleavage of the linking moiety is not unique to target celis, the greater cleavage achieved at or near target cells renders the cleavage selective for purposes of the present invention.

'Target cell refers to a tumor cell or to an endothelial cell involved in tumor neoangiogenesis.

entity, rendering it inactive until specifically released. The linking moiety is susceptible to specific, selective cleavage at or near a tumor or target cell. By virtue of the specific and selective cleavage of the linking moiety in vivo, an entity formulated as a prodrug. . .

Linking moiety

The linking moiety can comprise any molecule that is susceptible to specific cleavage at or near a tumor or a target cell. The linking moiety is covalently linked to the masking moiety and to the biologically active entity, thereby linking the two. . .

While not intending to be bound by theory of operation, it is believed that tumors and target cells secrete into the extracellular medium a factor or factors such as proteases or peptidases that are capable of specifically cleaving. in tumor neoangiogenesis excrete a significantly higher concentration of the factor thereby permitting specific and selective cleavage at or near tumors and/or target cells. The resulting improved selectivity of action of the biologically active entity is illustrated in FIG.

of biologically active entity 12 and linking moiety 14 is relatively stable at or near healthy cell 16. In FIG. 1 C, target (tumor or angiogenic endothelial) cell 18 secretes a factor 20 which is capable of specifically cleaving the linkage between linking moiety 14, liberating released biologically active entity 12'. Liberated biologically active entity 12' is free to exert its activity on target cell 18. For instance, biologically active entity 12' might bind receptor 22 on the surface of target cell 18, thereby initiating an intracellular cascade leading to the apoptosis or another form of death of tumor cell 18. Because. . .

Factor 20 can be any molecule or condition in the environment at or near target cell 18 that is capable of specifically cleaving linking moiety 14. While not intending to be bound by theory, it is believed that: factor 20 is a protease or peptidase selectively secreted by target cells. However, since all proteases or peptidases that specifically cleave the linking moiety have not yet been identified, factor 20 can. . . condition that is capable of specifically cleaving the linking moiety. For instance, factor 20 might even be low pH conditions near a target cell. Factor 20 is selectively present at or near target cells. It can be present at or near target cells exclusively, or it can be enriched at or near target cells such that: prodrug 8 is cleaved preferentially at

or near target celis and administration of prodrug 8 displays improved selectivity for target celis relative to administration of the naked biologically active entity 12 or released biologically active entity 12'.

Preferred linking moieties are peptides that are susceptible to specific cleavage at or near target celis. For example, it has been discovered that peptides having the amino SUBSTITUTE SHEET (RULE 26) acid sequence (Leu)<sub>y</sub>(Ala-Leu)<sub>x</sub>, Ala-Leu and peptides having. . . 0 or 1 and x = 11 2, or 3) are specifically cleaved by a factor in the extracellular milieu near target celis. Preferred peptide linking moieties comprise the amino acid sequence Ala-Leu-Ala-Leu (SEQ ID NO:1), Leu-Ala-Leu-Ala-Leu (SEQ ID NO:2), Leu-Ala-Leu (SEQ ID NO:3), . . .

#### 5.6 Biologically active entities

The biologically active entity can be any entity that has biological activity against tumors or target celis, or any entity that would derive an advantage from being selectively administered to a tumor or target cell. Preferred biologically active entities include those entities that are cytotoxic and/or cytostatic to tumors and/or target celis such as, for example TNFa, IFN- $\alpha$ , IFN- $\gamma$ , IL-1, IL-2, IL-6, an IGF-1 antagonist, a lytic peptide, an antiangiogenic peptide, a thrombospondin-derived. . .

adjusting the biologically active entity:linking moiety molar ratio of the conjugation reaction. Specific cleavage of the linking moiety in the vicinity of target celis such as tumor celis releases the biologically active polypeptide modified with a leucine residue or a phenylalanine residue at each amine. . .

Tumor selective prodrug of TNFa In one preferred embodiment of this aspect of the invention, a prodrug selectively delivers active TNIFa to target celis. TNFa can be linked to a masking moiety via any linking moiety of the present invention.

the surface of the majority of mammalian celis. Receptor aggregation upon TNIFa binding might be the mechanism for receptor activation in the target cells (Banner et al, 1993, Cell 73:431-445). For an extensive review on TNIFa, see Sidhu and Bollon, 1993, Pharmacol. Ther. 57:79. . .

stability and tissue distribution to the PEG-TNFa conjugates described above. However, since selective activation of the prodrug at or near tumors or target celis liberates leucyl-TI\&excl;Fa, the prodrug conjugates should display little or no loss of TNIFa specific activity in vivo. As a result, . . . ensuring reduced toxicity and allowing the

use of higher dose leveis. In acidition, selective activation of the prodrug at or near target celis should dramatically enhance the selectivity of the prodrug relative to the PEG-TNFa  
SUBSTITUTE SHEET (RULE 26)  
conjugates. The PEG-TNIFa conjugates displayed only. . .

aL, 1995, *supra*. Because the PEG or polymer masking moieties are specifically and selectively cleaved at or near a tumor or target cell, when formulated as a prodrug according to the invention, the TNFa can be completely inactivated by the PEG or polymer masked. . .

activated IGF-1 antagonist prodrug  
In another embodiment, a prodrug selectively delivers an oligopeptide antagonist of insulin-like growth factor QGF-1) to tumors or target celis in vivo. The masking moiety  
SUBSTITUTE SHEET (RULE 26)  
can be selected from any of the masking moieties discussed above, and.

the IGF-mediated survival function is likely to increase the antitumor effects of conventional chemotherapy  
(Gooch J. L. et aL, 1 999 , *Breast Cancer Res. Treat.* 56:1 -1 0).

1.3 Tumor activated prodrug of a thrombospondin-1 derived peptide  
In another preferred embodiment, a prodrug compound is capable of selectively delivering to target celis an antiangiogenic peptide derived from the structure of the angiogenesis inhibitor thrombospondin-1 (TSP-1).

embodiment of the invention, peptides derived from the primary sequence of TSP-1 are formulated as prodrug compounds for selective delivery to target cells. In particular, peptide sequences that comprise reverse sequences of D-amino acids derived from a type-1 repeat of amino acids from the. . .

substance P antagonist  
In another preferred embodiment of the invention, substance P antagonists are formulated as prodrug compounds for selective delivery to target celis.

Growth factors play an important role in the pathogenesis and evolution of cancers. New targets for therapy have been identified from the knowledge of the role such growth factors play in the progression of lung cancer.. . .

Accordingly, in this embodiment, substance P antagonists are formulated as prodrugs for selective delivery to target celis. A preferred substance P antagonist is a peptide with the amino acid sequence D-Arg-Pro-Lys-Pro-D-Trp-Gin-D-Trp-Phe-D-Trp-Leu-Leu-NH2 (SPD). Preferred masking moieties include biocompatible.

5 2.1 Tumor activated prodrug of a lytic peptide  
In another embodiment of the invention, a prodrug selectively delivers to target  
celis a peptide that is capable of lysing those celis in vivo. In this embodiment, a lytic peptide is finked to any. . .

Due to their intrinsic cytolytic activity, naked lytic peptides active on marnmalian cells are inherently toxic. They must be targeted specifically to tumor cefis in the form of prodrugs.

The transport peptide portion of the construct enables, facilitates or enhances transport of the intracellularly active entity into the target cell and/or nuclear transiocation of the entity. The action of any biologically active entity, including intracellularly active biologically active entities can potentially. . .

protein - carrier peptide prodrug

In this embodiment of the present invention, a prodrug selectively transports an intracellularly active, pro-apoptotic protein into target celis in vivo. A pro-apoptotic protein is formulated in a prodrug as a construct comprising the pro-apoptotic protein and a transport peptide.. . .

supra. Preferred masking moieties include PEG, preferred linking moieties incude the tetrapeptide Ala-Leu-Ala-Leu. When the prodrug is in the environment of a target cell, the linking moiety is cleaved liberating an active leucyl derivative of the active transport peptide. The transport peptide carries with. . . the cell. If so, the cleavage site can be cleaved within the cell liberating the intact, active pro-apoptotic protein within the target cell.

embodiments of the invention, the prodrug compounds are dual prodrugs. A dual prodrug compound can deliver two or more entities to target cells. In dual prodrugs, the biologically active entity is a cytostatic or cytotoxic entity as described in detail above. In addition, the. . .

the present invention incide any pair of entities that have a biological activity and a therapeutic effect on a tumor or target cell. For instance, a dual prodrug can comprise two biologically active polypeptides, two biologically active small molecules, two extracellularly active biologically active. . . Particulary useful prodrugs of the present invention are those that comprise a pair of entities that act in concert at a target cell. For instance, one of the entities can be a ligand for a cell surface receptor that facilitates transport of the other. . .

In a third pair, a small molecule and a polypeptide can have synergistic effects on the same target cell.

an amino group, such as a dicarboxylic acid (e.g., citraconyl, dimethylmaleyl, glutaryl, succinyl and diglycolyl). When placed in the vicinity of a target cell, dual prodrug 52 is cleaved to release 2 moles of released biologically active entity 39 for every mole of dual. . .

of TNFa or to abrogate the cellular resistance to TNFa. There is convincing evidence that there is a synergy between TNFa and topoisomerase-targeted drugs such as doxorubicin, VIVI-26, etoposide, teniposide and daunorubicin. This synergy is related to a rapid increase in specific activity of topoisomerase. . .

amino termina&ieq; end of the linking moiety via a dicarboxylic acid spacer. Activation of the prodrug in the vicinity of a target cell liberates leucyl-doxorubicin and TNFa modified with a portion of the linking moiety.

In the vicinity of target cefis, prodrug 40 is specifically cleaved to yield Compound 35 and released biologically active entity 39. Released biologically active entity 39. . .

Activation of the prodrug in the vicinity of a target cell liberates compound 48 comprising biologically active entity 38, spacing moiety 42 and a leucine residue. Again, the synthesis may be controlled. . .

the free carboxyl groups of compound 58 to yield dual prodrug 52. Cleavage of dual prodrug 52 in the vicinity of target celis liberates two molecules of released biologically active entity 39. Both molecules of released biological entity 39 comprise. . .

the invention can be used in a wide variety of applications to inhibit or prevent the growth of a tumor or target cell. For example, the prodrugs can be used to treat or prevent diseases related to tumor cell growth in humans and. . .

therapeutically effective amount is meant an amount of peptide or composition that inhibits the growth of, or is lethal to, a target cell. The actual therapeutically effective amount will depend on a particular application. An ordinarily skilled artisan will be able to determine therapeutically. . .

For use to treat or prevent tumor or target cell growth or diseases related thereto, the prodrugs of the invention, or compositions thereof, are administered or applied in a therapeutically effective. . . By therapeutically effective amount is meant an amount effective to ameliorate the symptoms of, or ameliorate, treat or prevent tumor or target cell growth or diseases related thereto. Determination of a

therapeutically effective amount is well within the capabilities of those skilled in the. . .

receptor-binding assays are carried out with the conjugates of TNFa to check inactivation as described, supra. Then, culture media conditioned by MCF-7/6 (breast carcinoma), LS T (colon carcinoma), LNCaP (prostate carcinoma) and NC1-H209 (small-cell lung carcinoma), or other cell lines are used to check the reactivation of the conjugates by tumor-released peptidases.. . .

dual TNFa - doxorubicin prodrug

In this example, we present a dual prodrug that releases TNFa and the antineoplastic entity doxorubicin at target cells in vivo.

The activities of the IGF-1 antagonist and its leucyl-derivative are compared in receptor binding and cell proliferation assays. MCF-7/6'human breast cancer cells are seeded and grown in serum-free medium. They are then incubated at 40C with [125I]-IGF-1 in the presence of increasing. . .

activity is compared to that: of Dox and of the IGF-1 antagonist, alone or in combination. Nude mice bearing MCF-7/6 human breast tumors are used for the activity assays.

- doxorubicin prodrug

In this example, we present a dual prodrug that specifically releases a lytic peptide and doxorubicin at or near target cells in vivo.

we describe the design and-preparation of an HIV Tat-derived transport peptide (Gly-Arg-Lys-Lys-Arg-Arg-Gln-Arg-Arg-Pro-Pro-Gin-Cys) prodrug

for carrying doxorubicin directly to the nucleus of a target cell. Formulation of, the

3 5 construct as a prodrug according to the present invention by coupling with PEG-Ala-Leu-  
SUBSTITUTE SHEET (RULE 26)

Ala-Leu provides selectivity for target cells to the construct and increases its stability. The

HIV- Tat-derived transport peptide of the construct carries doxorubicin to the nucleus. . .

The uptake of the biotinylated peptide and its leucyl-derivatives in MCF-7/6 human

breast cancer cells is determined after reaction with streptavidin-conjugated horse radish peroxidase. Cells are incubated for 1 to 18 hours with biotinylated. . .

centrifuged to eliminate cells and analyzed by HIPI-C. The disappearance of the conjugates over time is quantified. Media conditioned by MCF-716 (breast carcinoma) and LS-1 74-T (colon carcinoma) cell lines are used to check tumor peptidase reactivation of the conjugates. After incubation at 370C. . .

evaluation of its in vivo toxicity (lethality studies) and chemotherapeutic activity in nude mice bearing

subcutaneous  
resistant tumors such as the human breast cancer MCF-7/Adr.

14. Example 10: Pro-apoptotic protein-carrier peptide prodrug  
In this example, we describe a prodrug that selectively delivers a  
pro-apoptotic  
protein construct to target celis. The construct inciudes a  
transport peptide that carries  
the pro-apoptotic protein into the nucleus of the target cell  
and the pro-apoptotic protein  
granzyme B.

CLMEN. . . that  $(M - L1)_n$  hinders the activity of B and is susceptible to  
cleavage  
at or near a tumor or a target cell; and n is an integer from  
1 up to the total number of  
reactive groups of B.

each independently biologically active entities and L3 is a linking  
moiety susceptible to cleavage at or near a tumor or a target  
cell.

=>

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